REMARKS

Applicants have carefully considered this Application in connection with the Examiner's Action, and respectfully request reconsideration of this Application in view of the above amendments and the following remarks.

Claims 5, 6, and 8-15 are pending in this application.

Claim 14 has been amended to clarify that an antibody against a region of SRF comprising SEQ ID NO:5 is used in immunoblot analysis. This amendment is supported throughout the specification, particularly in paragraph [0297].

I. CLAIM REJECTIONS UNDER 35 USC §103

The Examiner has maintained the rejection of Claims 5, 6, and 8-15 under 35 U.S.C. 103(a) as being unpatentable over Drewett et al. (Journal of Biological Chemistry [2001] 276:36, 33444-33451, "the Drewett Reference") in view of Narula et al. (PNAS [1999] Vol. 96, 8144-8149, "the Narula Reference").

The Examiner states that it would have been obvious to one of skill in the art at the time the invention was made to combine the teachings of the Drewett Reference with the Narula Reference to develop a method of diagnosing cardiac disease in an individual comprising the step of identifying cleavage of SRF in at least one cell from a sample from said individual and that the Narula Reference indicates the relationship between apoptosis and heart failure, while the Drewett Reference describes the relationship between Serum Response Factor (SRF) cleavage and apoptosis.

Applicants respectfully disagree. Although it may seem clear to one familiar with the specification of the current application, it would not have been evident in the absence of the current disclosure that specific cleavage fragments from caspase-3 cleavage of SRF would be associated with human heart failure. There is no basis for combining the elements from these separate references to arrive at the claimed material, either in the references themselves, or within the knowledge of an ordinarily skilled artisan.

The Law on Obviousness with Respect to Unpredicatable Arts

The United States Supreme Court has held in *KSR International Co. v. Teleflex Inc.*, 127 SCt 1727; 167 Led2d 705 (2007), that "(w)hen there is design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill

has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." In the current case, however, the existence of a **vast multitude of genes related to apoptosis,** and an **unclear relationship between the each specific gene and the apoptotic process,** means that the prior art universe is not limited to "a finite number of identified, predictable solutions," as required for obviousness in *KSR*.

After the *KSR* decision, obviousness with respect to unpredictable arts was further discussed by the U.S. Court of Appeals for the Federal Circuit in *Ortho-McNeil Pharmaceutical Inc. v. Mylan Laboratories Inc.* 86 U.S. P.Q. 2d 1196 (Fed. Cir. 2008), wherein the Federal Circuit held that *KSR* "posits a situation with a finite, and in the context of the art, small or easily traversed, number of options that would convince an ordinarily skilled artisan of obviousness." In this case, the Federal Circuit, goes on to find that, since a person of ordinary skill would not have been likely to start with the lead compound identified in the patent at issue, and would not have had a reason to select a route which produced a specific intermediate from that lead compound, or to stop at that intermediate and test it for activity relating to a different disease state than the original purpose for development, there was "**clearly not the easily traversed, small and finite number of alternatives that *KSR* suggested might support an inference of obviousness.**" *Id.* at 1201. The Federal Circuit also disapproved the expert's "obviousness" testimony by saying " Mylan's expert, Dr. Anderson, **simply retraced the path of the inventor with hindsight, discounted the number and complexity of the alternatives, and concluded that the invention of topiramate** [the compound in suit] **was obvious.**" *Id.* Accordingly, the Federal Circuit determined that the compound claim is not obvious.

The application of these holdings to unpredictable biological and chemical arts including the field of the currently claimed invention, has also been discussed (again post- *KSR*) by the Federal Circuit in *Eisai Co. Ltd. v. Dr. Reddy's Laboratories Ltd.*, 87 U.S.P.Q.2d 1452 (Fed. Cir. 2008), wherein the Court stated that, "[to] the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on these 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." *Id.* at 1457.

In the present case, a skilled artisan would not have known that SRF cleavage in cardiac cells, and in particular detection using an antibody raised against SEQ ID NO:5, would be an indicator of cardiac disease. A skilled artisan might have accidentaly chosen SRF for further investigation, but he might also have chosen one of the many of other genes involved in the apoptotic cascade. The author of the Narula Reference describes the state of the art relating to the

understanding of the apoptotic cascade in human disease in the last full paragraph of the second column of page 8144, stating that:

> "(a)lthough sequential activation of the apoptotic cascade has been well characterized in nematodes, in cell culture, and in cell free systems, **little information is available in human diseases**. [Emphasis added]"

The Drewett Reference merely discloses the detection of 30-35 kDa fragments approximately half of the size of full-length SRF (page 33445, second column, seventh full paragraph), and identifies the antibodies as " N-terminal (α1122; M.E. Greenberg)" and "C-terminal (α1795; M.E. Greenberg)" (page 33445, second column, second full paragraph). It has not been demonstrated that the antibodies recognize the 12 residue SEQ ID NO:5. In order to clarify this difference in the claims, Applicants have amended Claim 14 to recite a region recognized by the antibody which comprises SEQ ID NO:5, as supported throughout the specification, particularly in paragraph [0297].

Thus, the skilled artisan might have chosen to use antibodies directed against **any** region within the SRF gene as a possible predictive marker once that gene had been selected.

Thus, the cited references do not present to the ordinarily skilled artisan an easily traversed, small and finite number of alternatives, because of the **following variables and alternatives** from which the artisan would be required to chose to arrive at the currently claimed invention:

- **Identity of the gene:** the artisan would have had to identify SRF as the gene to be detected, despite the author's statement in the Narula Reference that, with regard to the apoptotic cascade, there is "little information is available in human disease."
- **Specific cleavage fragments of SRF:** having chosen SRF, the artisan would have had to identify a particular cleavage site resulting in a particular fragment of SRF which was relevant to apoptosis specifically in cardiac disease rather than any other disease.
- **Antibody to be used in the detection:** the artisan would have had to identify an antibody which was capable of detecting the SRF cleavage products which can be found in cardiac cells.
- **Cell type:** the artisan would have had to identify a cell system in which to study the relationship between SRF cleavage and disease, given that the apoptotic cascade proceeds differently and involves different molecules in different cells types. This is evidenced by the fact that the authors of the Drewett Reference had to abandon their

studies in NIH3T3 cells due to the nature of the apoptotic mechanism in those cells (p. 33446, column 1, first full paragraph).

- **Disease state**: the artisan would have had to identify a disease state to relate to the SRF measurement, given that essentially any diseased or even healthy cell is capable of undergoing apoptosis, and that apoptosis is by no means limited to cardiac disease.

Therefore, none of the possible avenues for research described above provides a predictable outcome, as required by *KSR*. The **complex and incompletely understood pathway of molecules in the apoptotic cascade in human disease, and the fact that the cascade varies with cell type and disease state in the cell, means that even if a skilled artisan had chosen SRF and detection of the particular region of SRF described here, there would have been no assurance that it would have served as a useful predictive marker.**

As described below, Applicants respectfully submit that the current invention belongs to a field of unpredictable biological arts, which rarely present the "finite number of identified, predictable solutions" required by *KSR*.

Inventive Concepts of the Present Application

Applicants submit that there is at least one non-obvious concept disclosed for the first time in the current application. That is, that SRF cleavage is useful in diagnosing cardiac disease.

The instant specification shows for the first time that the cleavage of a region of SRF, detected using an antibody raised against an N-terminal region of SRF comprising SEQ ID NO:5, can be used to diagnose cardiac disease in an individual. Although it may have theoretically reasonable to attempt to detect cardiac disease by investigating various alterations to SRF, biological systems are notoriously complex, and there **was no reason to select this particular gene and this particular cleavage site as an indicator out of thousands of possibilities**. It could also have been, that SRF cleavage was only associated with apoptosis in human BJAB cells, or that SRF cleavage only played an important role when apoptosis is induced by Fas cross-linking. In such complex systems as biological systems, obvious to try is not sufficient to meet the standard for obviousness.

Disclosures of Cited References

The Examiner has stated in the Office Action mailed 9.18.07, that the Drewett Reference teaches that fragments of SRF generated by caspase cleavage fail to maintain expression levels supported by full-length SRF during apoptosis, that variations in the level of SRF fragments indicated that SRF cleavage might be a regulated event, and that the reference teaches analysis of SRF cleavage products in cells by immunoblotting with antibodies against the carboxyl-terminus or amino-terminus of SRF.

Applicants respectfully point out that the results of the Drewett Reference were obtained in a human mature B-cell line (BJAB cells), and that **all types of cells cannot be expected to respond in the same manner to stimuli**. This is demonstrated in the Drewett Reference itself on p. 33446, column 1, first full paragraph, which describes how NIH3T3 cells entered apoptosis with delayed and heterogeneous kinetics in response to staurosporine compared with BJAB cells, and that because of this the authors selected BJAB cells which could more easily be induced to undergo apoptosis. This shows that **different cell types can have different concentrations of key molecules and different reaction kinetics for the apoptotic process. Therefore, it cannot be said that apoptosis in human cardiac cells is predictable based on apoptosis in non-cardiac cells**.

The Examiner has stated in the Office Action mailed 9.18.07, that the Narula Reference teaches that apoptosis is a predictor of adverse outcomes in patients with congestive heart failure, and that demonstration of an activated apoptotic cascade in cardiomyopathy could provide the basis for novel interventional strategies, and that protease cleavage in the myocardial cytoplasmic extracts support the phenomenon of apoptosis in end stage heart failure.

Applicants disagree with the Examiner's assessment. Although the Narula Reference appears to show that under certain conditions apoptosis has been observed in failing human hearts, this **does not provide direct evidence that specific types of SRF cleavage also occur in these hearts**. Apoptosis **is a complex cascade of molecular interactions, and it is clear that apoptosis occurs differently in different cells based on differing concentrations of key molecules**. For example, as described in the Drewett Reference and discussed above, apoptosis occurs on a different kinetic timescale in NIH3T3 cells than BJAB cells because of the difference in concentration of Fas on the surface of the cells. Therefore, it is clear that the apoptotic cascade which occurs in the NIH3T3 cell is not precisely identical to the apoptotic cascade which occurs in the BJAB cells, and that different molecular interactions may be more prominent in one cell type than others.

In contrast, the present invention describes directly a method of diagnosing cardiac disease in an individual by measuring cleavage of SRF in a cardiac cell from the individual. The measurement of any particular biomarker is an unpredictable and sensitive technique, and biomarker pathways are complex and interwoven. **Just because a particular protein is activated under one set of conditions in an *in vitro* experiment, does not mean that it will show a similar profile in a human heart *in vivo*.** Extensive experimentation would have been required to develop the currently claimed material based on the cited references, and as described above, references may render a concept obvious only when there are a finite number of identified, predictable solutions, and a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. This is not the case in the present application.

Applicants therefore respectfully submit that the current claims are non-obvious, and request that the rejection be withdrawn.

II. CONCLUSION

Applicants respectfully submit that, in light of the foregoing Amendment and comments, Claims 5, 6, and 8-15 are in condition for allowance. A Notice of Allowance is therefore requested.

If the Examiner has any other matters which pertain to this Application, the Examiner is encouraged to contact the undersigned to resolve these matters by Examiner's Amendment where possible.

Respectfully submitted,

T. Ling Chwang
Reg. No. 33,590
Jackson Walker L.L.P.
901 Main Street, Suite 6000
Dallas, TX 75202
Tel: (214) 953-5959
Fax: (214) 661-6870

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